REMARKS

The Claim Amendments

Claims 70-75 constitute the pending claims in the present application.

Status of Application, Amendments, and/or Claims

Applicants thank the Examiner for indicating in the February 22, 2010 Advisory Action that Applicants' January 22, 2010 amendment was entered in full.

In the February 22, 2010 Advisory Action, the Examiner indicated that Applicants' arguments and amendments were persuasive, and thus that the enablement rejection was withdrawn, with regards to the breadth of subjects to be treated by the claimed method. However, the Examiner has maintained the remaining portion of the enablement rejection of claims 70-72 and 75 with regards to the alleged lack of working examples and the alleged and presumed ineffectiveness of the claimed method. The Examiner refused to enter or consider the evidence, in the form of several scientific research articles, that was submitted in the January 22, 2010 Response to address the still-rejected portion of the enablement rejection.

As the Examiner did not consider the evidence submitted with the January 22, 2010 Response or the arguments discussing that evidence, Applicants file herewith a Request for Continued Examination ("RCE"), a Response to the maintained rejections of the October 26, 2009 Final Office Action, and evidence to support the arguments made in this Response. Accordingly, Applicants request withdrawal of the finality of the outstanding Office Action, and consideration of the instant response and evidence.

Rejection of Claims 70-72 and 75 Under 35 U.S.C. § 112, 1st Paragraph

The Examiner has rejected claims 70-72 and 75 under 35 U.S.C. § 112, 1st paragraph, for allegedly failing to comply with the enablement requirement.

A. Applicants Are Not Required to Provide *in vivo* Examples

The Examiner alleges that the specification does not provide any *in vivo* working examples of treatment of a condition of abnormally enhanced vascular growth with a Sonic hedgehog blocking antibody. Applicants respectfully traverse.

Applicants maintain that the specification provides a working example, Example 4, that illustrates that a Shh blocking antibody inhibits vascular growth and erythropoiesis in whole mouse embryonic cultures. Applicants contend that this, taken in combination with the level of skill in the art, is sufficient to enable the skilled artisan to practice the claimed method. Satisfaction of the enablement requirement does not turn on the presence or absence of working examples. See, *e.g.*, MPEP 2164.02.

As previously discussed in Applicants' June 25, 2008 and April 13, 2009 Responses, it was well understood by the skilled artisan at the effective filing date, as it is well understood by the skilled artisan today, that inhibition of the blood supply feeding a tumor could be used as a treatment for cancer. Applicants maintain their arguments, as put forth in the previously filed Responses, that the claimed method does not rely on targeting tumor cells *per se*. Rather, the claimed method targets the vascular growth that accompanies the tumor, thereby making the claimed method beneficial across a range of tumors of diverse etiology. As it was known in the art as of the effective filing date of the instant application that inhibition of vascular growth was a beneficial treatment for tumors, Applicants' specification need not provide a detailed description of this information. See, *e.g.*, MPEP § 2163(II)(A)(2).

As further evidence that the skilled worker would have no difficulty in understanding how to use the claimed method, Applicants direct the Examiner to Valone *et al.* (Journal of Clinical Oncology, 1995, 13(9): 2281-2292-Exhibit A) and Weiner *et al.* (Cancer Research, 1995, 55:4586-93-Exhibit B). These documents teach methods of treating breast cancer patients by administering an antibody therapeutic. More importantly, these documents demonstrate that, at the filing date of the instant application, the skilled worker was aware of several means of preparing therapeutic antibody formulations, administering antibody treatments, determining appropriate antibody doses and analyzing antibody treatment efficacy in subjects suffering from breast cancer, a disease associated with excess vascularization and neovascularization. In view of the level of skill in the art and the teachings of the present application, one of skill in the art could practice the claimed invention without undue experimentation.

For all of the reasons above, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

B. The Application Provides an Enabling *in vitro* Example

The Examiner contends that the application allegedly does not provide any *in vitro* example that correlates with *in vivo* treatment. Specifically, the Examiner argues that Example 4 in the pending application allegedly can only be used to analyze hematopoiesis and not vasculogenesis.

i. *Embryonic Hemoglobin Is A Marker Used to Assess Vasculature*

The Examiner argues that ε-globin, an embryonic hemoglobin used as a marker for vasculogenesis in Example 4, allegedly is a marker only for hematopoiesis and not for vascular growth.

The Examiner acknowledges that the specification indicates that the Examples section relates to both hematopoiesis and vasculogenesis. However, despite this acknowledgement, the Examiner argues that this is "speculative". Despite the Examiner's further acknowledgement that hemoglobin was often used at the filing date of the instant application to assess angiogenesis in adult tissue, the Examiner alleges that there is no evidence that ε-globin was used to assess embryonic vasculogenesis. Applicants respectfully traverse.

Contrary to the Examiner's assertions, embryonic hemoglobin was used as a marker for vasculogenesis at the filing date of the pending application. Applicants direct the Examiner to Thompson *et al.* (Int. J. Microcirc.: Clin Exp, 1987, 6: 343-357- Exhibit C), which teach several different assays for assessing angiogenesis in embryonic tissue, including the analysis of embryonic hemoglobin content. Thompson *et al.* teach that a 21% increase in hemoglobin content of the embryonic chick chorioallantoic membrane 4 days after histamine is consistent with an overall increase in vasculature. See, *e.g.*, Abstract and page 348, first full paragraph. Therefore, Thompson *et al.*, support Applicants' contention that evaluation of embryonic hemoglobin levels can be used to assess vasculogenesis in embryonic cultures. Using the teachings of Thompson *et al.*, combined with the teachings of the specification and of the documents discussed in Applicants' April 13, 2009 Response, the skilled worker would understand that embryonic hemoglobin, *e.g.* ε-globin, may serve as a useful marker for angiogenesis. Accordingly, Applicants maintain that the working examples of the present application support methods of modulating both hematopoiesis and vasculogenesis.

ii. *Shh Plays a Role in Tumor Angiogenesis*

The Examiner acknowledges the connection between inhibition of vascular growth and therapeutic treatment of tumors. However, the Examiner contends that vascular growth allegedly does not necessarily involve Shh, and that there is allegedly no evidence in the relevant art that Shh plays a role in tumor angiogenesis independent of tumor expression of Shh. Applicants respectfully traverse.

Contrary to the Examiner's assertions, independent post-filing research studies support Applicants' unique findings establishing a link between Shh signaling and vascular growth. For example, Soletti *et al.* (Carcinogenesis, 2009, 30(4): 580-588-Exhibit D) teach that microparticles, small plasma membrane particles released by tumor cells or by blood and vessel wall cells, harboring Shh peptides were sufficient to induce angiogenesis *in vitro* through the upregulation of various pro-angiogenic factors. Thus, Soletti *et al.* support Applicants' teaching that tumor-associated excess vascularization or neovascularization involves Shh signaling, such as excess vascularization associated with a tumor.

iii. *Embryonic Cultures Are Commonly Used To Study Angiogenesis in Later Development*

The Examiner acknowledges that Palis *et al.* (Blood, 1995, 86(1):156-63), as discussed in Applicants' April 13, 2009 Response, teach an embryonic culture system for the purpose of studying vascular networks. However, the Examiner argues that embryonic cultures allegedly are not used as a model for excess neovascularization in later development. Specifically, the Examiner contends that the relevant art teaches a distinction between vasculogenesis in embryonic development and angiogenesis in later tissues, and that such teachings undermine the use of embryonic systems to study angiogenesis. Applicants respectfully traverse.

Contrary to the Examiner's assertions, embryonic culture systems often were used at the filing date of the instant application for the purpose of understanding angiogenesis in later development. See, *e.g.* Allen *et al.* (J. Anat., 1993, 183:579-585-Exhibit E), the abstract, which state that embryonic "chick area vasculosa capillaries bear similar structural and growth characteristics to those associated with tumour angiogenesis and suggest that they may prove to be a useful model system for studying the factors involved in pathological angiogenesis". See,

also, *e.g.*, Ribatti *et al.* (Int. J. Dev. Biol., 1996, 40:1189-97-Exhibit F), last paragraph on page 1194 and first paragraph on page 1195, which discuss chick embryonic chorioallantoic membrane as a useful model for identifying compounds that inhibit tumor-associated angiogenesis. These documents not only demonstrate the skilled worker's understanding that embryonic culture systems, as used in Example 4, are useful models for the purpose of studying angiogenesis in later development, these documents also teach that embryonic culture systems are useful for studying tumor-associated angiogenesis.

iv. *Enabling In Vitro Example: Conclusion*

For all of the reasons above, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

C. The Pending Claims Are Enabled For the Treatment of Solid Tumors Using a Shh Blocking Antibody

The Examiner alleges that the post-filing date art demonstrates that many solid tumors are not characterized by dysfunctions that lead to Shh overexpression, and that the claimed invention allegedly would be ineffective in inhibiting excess vascularization or neovascularization of those tumors. Applicants respectfully traverse.

Applicants maintain the arguments put forth in Applicants' June 25, 2008 and April 13, 2009 Responses, that the claimed invention is not based on necessarily modulating hedgehog signaling in tumor cells, but rather on inhibiting enhanced vascular growth, such as the vascular growth accompanying a solid tumor. While not all tumors overexpress Shh, vascular growth is still a crucial process in the development of many malignant solid tumors. Without angiogenesis, a solid tumor would be limited in its overall growth capacity and likely would be unable to metastasize. As demonstrated in Applicants' previous Responses, this concept was well understood in the art prior to Applicants' effective filing date. Therefore, while Shh overexpression may not be observed in all tumors, angiogenesis, which itself can be inhibited using an antagonist of hedgehog signaling, is a necessary component for development and maintenance of malignant solid tumors. Accordingly, based on the teachings of the instant application, one of skill in the art would appreciate that blocking Shh signaling by administering a Shh blocking antibody would inhibit the angiogenesis or neovascularization that is observed in

many developing solid tumors – regardless of whether the tumor itself is characterized by misregulation in hedgehog signaling.

However, despite these arguments, the Examiner has repeatedly pointed to U.S. Pre-Grant Application Publication 2004/0110663 ("the '663 publication") as supposed support for his contention that a Shh-blocking antibody would be ineffective in inhibiting tumor-associated angiogenesis or neovascularization in tumors that do not express Shh. The '663 publication describes an experiment involving the administration of the Shh blocking antibody 5E1 to a xenograft mouse model that was generated using the cancer cell line SW480 – a cell line that is not characterized by expression of Sonic hedgehog. The authors of the '663 publication conclude that the 5E1 antibody did not effectively inhibit the growth of the solid tumor. However, this experiment simply does not address the question of whether the Sonic hedgehog antibody inhibited vascular growth associated with the tumor.

The Examiner indicates that he was not persuaded by the arguments and evidence of record, and continues to argue that Applicant's argument is a "hypothetical" argument allegedly unsupported by evidence. However, as detailed above and in Applicants' previous response, Applicants have provided evidence to support the conclusion that the experiment provided in the '663 publication is simply not relevant to assessing enablement of the claimed methods because the experiment did not examine angiogenesis or otherwise report data to allow conclusions regarding any effect (or lack of effect) on angiogenesis.

In view of the forgoing, Applicants contend that the '663 publication fails to undermine the patentability of the claimed invention. Accordingly, there is no evidence of record to counter or undermine the arguments and evidence presented in support of Applicants' position that the claims are enabled throughout their scope. Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

D. **Enablement Rejection: Conclusion**

For all of the reasons discussed above, the amended claims are enabled by the application as filed. Applicants respectfully request that the Examiner reconsider and withdraw the Enablement rejection.

Co-Pending Applications

The following co-pending applications have already been brought to the Examiner's attention and made of record during prosecution of this application: application serial number 10/727,195; application serial number 09/977,864; and application serial number 10/652,298. Applicants also direct the Examiner to application serial number 12/728,948. Prosecution in the co-pending applications is on going and Applicants invite the Examiner to consider all prior, current, and future prosecution in the co-pending applications.

The most recent action in application serial number 10/727,195 is an Issue Notification mailed on March 17, 2010. The most recent action in application serial number 09/977,864 is a non-final Office Action mailed on December 4, 2009. The most recent action in application serial number 10/652,298 is an Issue Fee Payment filed on March 3, 2010. Application serial number 12/728,948 was filed on March 22, 2010 and has not yet undergone substantive examination.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our **Deposit Account No. 18-1945, under Order No. HC-P02-060**.

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Respectfully Submitted,
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